## REMARKS

The present invention relates to antibodies that specifically bind to cardiac specific troponin I in both free and complexed forms. In particular, the instant claims relate to antibodies that are insensitive with respect to each cardiac troponin I form selected from the group consisting of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T; to methods for selecting such insensitive antibodies; and to compositions comprising such insensitive antibodies. Such antibodies may be provided on solid phases and as members of an antibody pair comprising a solid phase antibody and a labeled antibody.

Claims 69-74 and 79-93 are pending in the instant application. The Examiner has indicated in Paper No. 15 that claims 71-74 are allowed, and that claims 84, 85, 90, and 93 would be allowable if written in independent form. In response, Applicants have cancelled claims 84, 85, 90, and 93 herein, and added new claims 94-98 to provide corresponding independent claims. In addition, claims 79-81 and 88 (including 94-98) have been amended herein in order to clarify that the one or more antibodies referred to in the claims each are selected to bind to cardiac troponin I. Applicants respectfully submit that the amendments do not alter the scope of the claims, but are merely offered to clarify the claimed subject matter for the benefit of the Examiner. The amendments find basis throughout the application and raise no issue of new matter.

Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer or not yet claimed in one or more applications that may claim priority hereto. Applicants respectfully request reconsideration of the rejected claims in view of the following remarks.

35 U.S.C. § 112, First Paragraph, Enablement Rejection

The only rejection remaining in the instant case is based on an alleged lack of enablement with regard to claims 69, 70, 79-83, 86-89, and 91-92. Applicants respectfully traverse this rejection. Applicants disagree that the specification, which the Examiner acknowledges is

enabling with regard to a cocktail of antibodies that are insensitive for each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T, is not enabling with regard to a single antibody that binds to each of the recited cardiac troponin I forms.

The standard for determining enablement is whether the specification as filed provides sufficient information as to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In responding to the previous office action, Applicants noted that the enablement rejection was based entirely upon the unsupported opinion of the Examiner. As such, the Examiner has not established any reasonable basis for questioning the enablement of the claims. *See*, MPEP § 2164.04 (the examiner has the initial burden of establishing a reasonable basis to question enablement; it is incumbent on the Patent Office to explain why it doubts any statement in a disclosure, and to back up its assertions with acceptable evidence or reasoning).

In addition, Applicants also provided a declaration of one of skill in the art, Dr. Kenneth F. Buechler, as further evidence of enablement of the claimed invention. In the declaration, Dr. Buechler provided a reasoned scientific explanation as to why the skilled artisan, using only routine methods that are well known in the art, could practice the instantly claimed invention. The Examiner has simply dismissed this scientifically-based explanation, stating "Applicant fails to provide evidentiary showing such as in the form of data, that supports generation [of the antibodies of the claims]." Paper No. 15, page 10.

Applicants respectfully submit that, by dismissing Applicants' evidence, the Examiner has improperly failed to consider the evidence as a whole, a consideration that is required in any

determination of enablement. As stated in MPEP § 2164.05, a declaration or affidavit is, itself, evidence that must be considered. Furthermore, the evidence need not be conclusive, but merely convincing to the skilled artisan. *Id.* In contrast, the Examiner applies an improper standard for proof of enablement, requiring that conclusive evidence that the antibodies of the claims have been generated be provided by Applicant. *See, e.g.*, Paper No. 15, page 10, second full paragraph.

The declaration of Dr. Buechler is supported by sound scientific reasoning. In contrast, the Examiner's comments concerning the invention are based solely on personal opinion. As stated in MPEP § 2164.05, the Examiner must never make a determination concerning enablement based on the Examiner's personal opinion (emphasis in original). Applicants respectfully submit that the following analysis of the factors set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1998) demonstrates that the present claims meet the enablement standard of 35 U.S.C. § 112.

*Nature of the Invention*

The present invention is directed to providing one or more antibodies that are insensitive with respect to each cardiac troponin I form selected from the group consisting of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T; to methods for selecting such insensitive antibodies; and to compositions comprising such insensitive antibodies.

In contrast, the Examiner continues to maintain that "the invention is directed to a cocktail of insensitive antibodies which bind each one of the free, binary complex, and ternary complex isoforms of [cardiac troponin I] (Paper No. 15, page 3, emphasis added), despite the fact that the specification as filed states explicitly that the use of a cocktail of antibodies for this purpose is but one embodiment of the instant invention. For example, the specification explicitly states:

> "[t]he immunoassay may be formulated with a cocktail of antibodies to bind all the troponin complexes and the free troponin I and T. Alternatively, the immunoassay can be formulated with specific antibodies that recognize epitopes of the troponin I and T in the complexes and also the unbound troponin I and T. A

> preferred immunoassay for troponin I or T involves conjugation of an antibody or a cocktail of antibodies to a label or signal generator to form an antibody conjugate(s), which are capable of binding to cardiac specific regions of the troponin complexes of troponin I or T and to unbound troponin I or T.

Page 24, line 21, through page 25, line 3. This section and others in the specification clearly indicate that the invention is not limited to "cocktails" of antibodies, as the Examiner contends, but rather to providing one or more antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T.

Applicants also submit that the Examiner's reply to Applicants' arguments in this regard appear to contradict the Examiner's own position. Indeed, the Examiner acknowledges in Paper No. 15, page 9, first full paragraph, that "page 6 of the specification provides that an 'insensitive antibody' is one that will tend to bind more than one form of troponin, i.e. each one of free cTnI, cTnI in a binary complex with troponin C, and cTnI in a ternary complex with troponin C and troponin T, as recited in the claims." It is unclear, therefore, why the Examiner continues to maintain that the invention is directed solely to providing "a cocktail of antibodies." Applicants respectfully submit that the Examiner's statement of the "nature of the invention" is without support of any evidence of record.

*State of the Prior Art*

Both Applicants and the Examiner acknowledge that the prior art fails to disclose any antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T. However, methods for producing antibodies to an antigen of interest are well established in the art.

*Level of one of Ordinary Skill*

Both Applicants and the Examiner acknowledge that the level of skill in the art of antibody preparation is high.

*Predictability in the Art*

As discussed above, Applicants have provided a declaration of one skilled in the art, Dr. Kenneth F. Buechler, providing a reasoned scientific basis as to why the skilled artisan would reasonably believe that it would be predictable that antibodies could be obtained that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T. As discussed in the declaration, cardiac specific troponin I contains various antigenic sites. Because certain antigenic sites may remain available for antibody binding regardless of the complex state of troponin I, these sites may be used to bind free troponin I as well as troponin I complexed with troponin C and/or troponin T. Nothing of record, other than the Examiner's opinion, contradicts this reasoned scientific conclusion.

Moreover, the examples described in the instant invention confirm the accuracy of the scientific basis for Dr. Buechler's statements. For example, Example 23, on page 87, line 31, through page 88, line 2, of the specification, describes the selection of antibodies that bind to both free troponin I and to troponin I in a ternary complex with troponin C and troponin T. According to Dr. Buechler, the skilled artisan would understand that antibodies which bind to free troponin I and to troponin I/C/T ternary complex would also be expected to bind to the binary complex of troponin I and troponin C, because the site on troponin I to which the antibody binds was not blocked by the presence of troponin C in the ternary complex. *See, e.g.*, drawing on page 3, of Buechler declaration.

Furthermore, while the declaration of Dr. Buechler indicates why the skilled artisan would reasonably believe that even a monoclonal antibody could be produced having the

requisite specificity, the instant claims are not limited to a monoclonal antibody having a single binding specificity. Instead, the instant specification states on page 8, lines 9-12, that an antibody may also be a polyclonal antibody. The skilled artisan would understand that a polyclonal antibody that binds to each of free troponin I, the troponin I/troponin C binary complex, and the troponin I/troponin C/troponin T ternary complex could readily be obtained by immunization of an animal with each of these troponin I forms as described in the specification, *e.g.*, on page 21, lines 3-32, and isolating the antibodies produced. Methods for generating polyclonal antibodies have long been well known in the art. *See, e.g., id.*

In contrast to the evidence of predictability in the art provided by Applicants, the Examiner offers only the conclusory statement that "there is no predictability" in the art. *See, e.g.*, Paper No. 15, page 4, second paragraph. Such a conclusory statement does not establish a reasonable basis for questioning the enablement provided in the specification. *See*, MPEP § 2164.04 (the examiner has the initial burden of establishing a reasonable basis to question enablement; it is incumbent on the Patent Office to explain why it doubts any statement in a disclosure, and to back up its assertions with acceptable evidence or reasoning). Furthermore, as discussed above, the Examiner simply dismisses the scientific explanation provided by Dr. Buechler, and applies an improper standard for proof of enablement, requiring that conclusive evidence that the antibodies of the claims have been generated be provided by Applicants.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge that it would be predictable that the antibodies of the instant claims could be obtained using only routine immunological methods.

*The Amount of Direction or Guidance Present*

The instant specification provides extensive guidance as to how antigens should be prepared, and how antibodies should be screened, in order to obtain antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T. *See, e.g.*, specification,

page 21, line 3, through page 24, line 3; Example 22 beginning on page 82; and Example 23, beginning on page 87.

In contrast, the Examiner offers only the conclusory statement that "the specification fails to provide guidance to provide a single insensitive antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI." *See, e.g.*, Paper No. 15, page 4, third paragraph. Again, such a conclusory statement does not establish a reasonable basis for questioning the enablement provided in the specification. Moreover, the Examiner's reply to Applicants' arguments that "nowhere in the specification specifically shows... any generation and selection [of such antibodies]" (Paper No. 15, page 11, first full paragraph) applies an improper standard for proof of enablement, requiring that conclusive evidence that the antibodies of the claims have been generated be provided by Applicant. The question is not whether such antibodies have been generated, as the Examiner suggests; rather, the question is whether the specification enables such antibodies to be generated without undue experimentation. Furthermore, as discussed in the following section of this submission, the Examiner is incorrect that no such antibodies are demonstrated in the specification.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge the extensive guidance provided by the instant specification.

*Presence of Working Examples*

As discussed by Applicants previously, Example 23 describes antibodies and assays that measure both free and ternary complexes of troponin I. Because these antibodies rely on formation of a sandwich of (labeled antibody)-(analyte)-(biotinylated antibody)-(avidin solid phase) for development of an assay signal, the skilled artisan would acknowledge that both the biotinylated and labeled antibodies must bind to both free and ternary troponin I complexes. Further, because the site on troponin I to which the antibody binds was not blocked by the presence of troponin C in the ternary complex, the skilled artisan would understand that such antibodies would also be expected to bind to the binary complex of troponin I and troponin C.

Thus, the instant specification provides working examples of antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T.

The Examiner's reply indicates that the Examiner disagrees with this reasoning, which is based on evidence of record and sound scientific principles. However the Examiner provides no evidence or reasoning that is inconsistent with this evidence. Instead, the Examiner again simply asserts that nowhere in the examples is such an antibody "specifically" provided. Paper No. 15, page 12, first full paragraph. As stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

Considering the objective evidence of record in its entirety, the skilled artisan would acknowledge that working examples of antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T are provided by the instant specification.

*Quantity of Experimentation Necessary*

As described in detain in the Buechler declaration and in Applicants' prior response, methods for preparing and identifying antibodies that are insensitive with respect to each of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T are described in detail in the instant specification. The Examiner does not disagree that methods for producing antibodies generally have long been well known and considered routine by those of skill in the art. Taken together, Applicants respectfully submit that the quantity of experimentation necessary is not undue.

In contrast, the totality of the Examiner's analysis of this point is to assert without support a conclusion that "it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed." Paper No. 15, page 5, first full paragraph. Again, such an assertion, unsupported by any evidence or reasoning of record, cannot establish a lack of

enablement. Moreover, in response to Applicants' arguments in this regard, the Examiner again relies on an assertion that nowhere in the examples is such an antibody actually provided. Paper No. 15, page 13, first paragraph. Again, evidence of enablement need not be conclusive, but merely convincing to the skilled artisan. MPEP § 2164.05. Finally, as discussed in the previous section of this submission, the Examiner is incorrect that no such antibodies are demonstrated in the specification.

*The Instant Claims Meet the Enablement Standard of 35 U.S.C. § 112, First Paragraph*

In view of the objective evidence of record, and the foregoing analysis of the factors set forth in *In re Wands*, Applicants respectfully submit that that the present claims meet the enablement standard of 35 U.S.C. § 112, and request that the rejection be reconsidered and withdrawn.

Examiner's Remarks Concerning the Meaning of the Phrase "an antibody"

On page 13, section F, the Examiner appears to take issue with a statement in the declaration of Dr. Kenneth F. Buechler, which stated that the phrase "an antibody" does not refer to a single molecule of antibody, but rather is understood in the art to refer to a single population of antibody. The Examiner asserts in reply that "an antibody" denotes "a singular form of an element." As discussed above, a declaration or affidavit is, itself, evidence that must be considered. In contrast, the Examiner has cited no evidence for the Examiner's interpretation of the phrase. Applicants also note that the term "antibody" is commonly used in the art to refer to for a plural form of an element. For example, a polyclonal antibody, which is a mixture of individual antibody molecules having a variety of specificities, is not "a singular form of an element." Likewise, the phrase "monoclonal antibody" is used to refer to a plural form of a single molecular element. Applicants respectfully request that the Examiner cite some objective evidence in support of the Examiner's interpretation of the phrase "an antibody," or withdraw the remarks.

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## CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date June 24, 2003

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